# PROCESS FOR THE ENANTIOSELECTIVE PREPARATION OF SULFOXIDES DERIVATIVES.

The present invention concerns a method of enantioselective preparation of substituted derivatives of sulfoxides, and more particularly a method of enantioselective preparation of compounds such as the enantiomers of tenatoprazole and other similar compounds.

Several derivatives of sulfoxide, and particularly of pyridinyl-methyl-sulfinyl benzimidazoles are known to be useful in therapeutics, acting as drugs endowed with properties which inhibit proton pump, that is to say drugs that inhibit the secretion of gastric acid and are useful in the treatment of gastric and duodenal ulcers. The first known derivative of this series of proton pump inhibitors is omeprazole, or 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, described in Patent No. EP 005.129, which is endowed with properties which inhibit the secretion of gastric acid and is widely employed as an anti-ulcerant in human therapy. Other derivatives of benzimidazole are known by their generic names, for example rabeprazole, pantoprazole, lansoprazole, and all exhibit structural analogy and belong to the group of pyridinyl-methyl-sulfinyl-benzimidazoles.

Tenatoprazole, that is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]imidazo[4,5-b]pyridine, is described in Patent No. EP 254.588. It is also part of the drugs considered as proton pump inhibitors, and it can also be used in the treatment of gastro-oesophageal reflux, digestive bleeding and dyspepsia.

All these compounds are sulfoxides presenting with asymmetry at the sulphur atom, and may therefore take the form of a racemic mixture of two enantiomers. It may be useful to separate them selectively in the form of any one enantiomer with *R* and *S* configurations, or (+) or (-) respectively, with specific properties that may be significantly different.

Several methods have been described in scientific literature to prepare either one of the enantiomers of these sulfoxides in a selective or predominant manner, especially omeprazole and its enantiomer of *S* configuration, esomeprazole, as well as its salts such as the sodium salt or magnesium salt.

Thus, Patent No. EP 652.872 describes the preparation method for the magnesium salt of the (-) enantiomer of omeprazole using its ester comprising a chiral acyloxymethyl group, separation of the diastereoisomers and solvolysis in an alkaline solution. US Patent No 5.776.765 describes a method which uses the stereoselective bioreduction of the racemic mixture of sulphide in the corresponding sulfoxide, using a microorganism containing a DMSO reductase, which enables to obtain a mixture that is considerably enriched with the (-) enantiomer, compared to the (+) enantiomer. US Patent No. 5.948.789 concerns the enantioselective preparation of sulfoxides, and particularly of the (-) enantiomer of omeprazole or of its sodium salts, via oxidation of the corresponding sulphide by a hydroperoxide in the presence of a titanium complex and of a chiral ligand. The method described in this patent makes it possible to obtain a mixture that is enriched with either one of the (-) and (+) enantiomers, according to the ligand used.

Works conducted so far by the applicant have showed that enantiomers of sulfoxide derivatives, and especially of tenatoprazole, can be obtained in an enantioselective manner under good purity and yield conditions, by enantioselective oxidation of the corresponding sulphide in the presence of a specific tungsten- or vanadium-based catalyst.

The present invention thus concerns an enantioselective preparation method for derivatives of sulfoxides presenting with asymmetry at the sulphur atom, producing either one of the enantiomers at a satisfactory level of yield and purity.

More particularly, this invention concerns a method of preparation which could produce in a noticeably enantio-

selective manner the (-) and (+) enantiomers of tenatoprazole. The terms "in a noticeably enantioselective manner" used above means that the desired enantiomer is obtained in a selective manner or in predominant quantities compared to the other enantiomer.

According to the method of preparation of the invention, an enantioselective oxidation of a sulphide represented by the following general formula (I)

$$A - CH_2 - S - B \qquad (I)$$

in which A is a pyridyl nucleus substituted in different ways and B a heterocylic residue comprising a benzimidazole or imidazo-pyridyl nucleus,
is carried out using an oxidizing agent in the presence of a tungsten- or vanadium-based catalyst and a chiral ligand, followed by salt formation by a base, if necessary.

In the general formula (I) hereabove, A represents preferably a pyridyl group or a pyridyl group bearing one or more substitutuents selected from the linear or branched alkyl groups of 1 to 6 carbon atoms, linear or branched alkoxy groups of 1 to 6 carbon atoms, methyl or ethyl groups substituted by one or several halogen atoms, amino, alkylamino or dialkylamino groups where the alkyl moiety, whether linear or branched, comprises of 1 to 5 carbon atoms; B represents a heterocycle selected from the benzimidazole or imidazo-[4,5-b]-pyridyl groups, substituted if necessary by one or several linear or branched alkyl groups of 1 to 6 carbon atoms, linear or branched alkoxy groups of 1 to 6 carbon atoms, and preferably substituted on one or several carbons by a methyl, ethyl, methoxy or trihalomethyl group.

In the general formula (I) here-above, A is preferably a 2-pyridyl group substituted by one or several methyl, ethyl, methoxy or trifluoromethyl groups, and more particularly a 4-methoxy-3,5-dimethyl-2-pyridyl group. B is preferably a 5-methoxy-1H-benzimidazolyle group or a B 5-methoxy-imidazo-[4,5-b]-pyridyl group.

The sulphide corresponding to the formula (I) here-above is a known product that can be prepared according to several methods described in literature, and for example, according to the methods described in Patents No. EP 254.588 and EP 103.553.

A sulfoxide is thus obtained which has the following formula

$$A - CH_2 - SO - B \qquad (Ia)$$

wherein A and B have the definition given above.

The oxidant used in the method of the invention is preferably a peroxide, hydrogen peroxide for example, or a hydroperoxide, cumene or tertiobutyl hydroperoxide for example. According to an advantageous method of implementation, highly concentrated hydrogen peroxide, higher than 30% for example, or a hydrogen peroxide complexed with urea (UHP : urea hydrogen peroxide $H_2NCONH_2.H_2O_2$), herein after called « UHP ») is used.

The tungsten- or vanadium-based catalyst is an essential element of the method of the invention which allows for the reaction to take place and for the desired derivative to be obtained with a good yield. According to the invention, a catalyst such as a V oxo-vanadium complex, prepared from vanadium acetylacetonate $VO(acac)_2$, for example, or else a derivative of tungsten such as tungsten trioxide $WO_3$, is preferably used. Such catalysts are commercially available. A complex prepared from vanadium sulphate $VOSO_4$ can also be used.

The choice of the ligand constitutes another characteristic element of the invention since it allows for the reaction to be selectively directed towards the desired enantiomer.

According to the present invention, in the case of a vanadium-based catalyst, the ligand is preferably tridentate.

The ligand can be advantageously represented by the following general formula (II):

$$RO-CR_1R_2-CR_3R_4-NR_5R_6 \qquad (II)$$

where **R** is a hydrogen atom or a linear or branched alkyl group of 1 to 6 carbon atoms or an aryl or heteroaryl group ;

$\mathbf{R_1}$ to $\mathbf{R_4}$, which can be the same or different, represent a linear or branched alkyl group of 1 to 6 carbon atoms, possibly comprising a heteroatom such as sulphur, nitrogen and oxygen and/or substituted by an amino group; an aryl group; an alkylaryl group; an alkoxycarbonyl group ; a heteroaryl group or a heterocyle ; or a heteroarylalkyl or a heterocyclalkyl group, with the proviso that $R_1$ should not be identical with $R_2$, and/or $R_3$ should not be identical with $R_4$, so that the ligand comprises one, or two asymmetry centers ;

$\mathbf{R_1}$ and $\mathbf{R_2}$ together can represent a carbonyl group C=O ;

$\mathbf{R_1}$ and $\mathbf{R_3}$, or $\mathbf{R_2}$ and $\mathbf{R_4}$ together, can form a carbon ring having 5 or 6 carbon atoms or a bicyclic system with 9 or 10 carbon atoms where one of the cycles can be aromatic ;

Similarly, $\mathbf{R_4}$ and $\mathbf{R_5}$ can form a 5- or 6-membered heterocycle with the nitrogen atom ;

$\mathbf{R_5}$ and $\mathbf{R_6}$, whether identical or different, represent a linear or branched alkyl group of 1 to 6 carbon atoms or a 5 or 6-membered carbon ring, or form a heterocycle with the nitrogen atom to which they are bound, or $\mathbf{R_5}$ and $\mathbf{R_6}$ represent, together with the nitrogen, a -N=CHAr double bond where **Ar** is a aryl residue, possibly substituted by 1 to 3 groups, and preferably bearing a hydroxyl group.

Preferably, **Ar** is a 2'-hydroxyphenyl group possibly substituted on the aryl group.

$\mathbf{R_1}$ and $\mathbf{R_3}$, or $\mathbf{R_2}$ and $\mathbf{R_4}$, represent preferably a hydrogen atom, whereas $\mathbf{R_2}$ and $\mathbf{R_4}$, or $\mathbf{R_1}$ and $\mathbf{R_3}$, respectively, are linear or branched alkyl groups of 1 to 6 carbon atoms, a aryl group or form together a carbon ring having 5 or 6 carbon atoms or a bicyclic system with 9 or 10 carbon atoms where one of the cycles can be aromatic.

According to the present invention:

- an « aryl group » means preferably a mono- or poly-cyclic ring system having one or more aromatic rings including

phenyl group, naphtyl group, tetrahydronaphtyl group, indanyl group and binaphtyl group. The aryl group may be substituted by 1 to 3 substituants chosen independently ones of the others among an hydroxyl group, a linear or branched alkyl group containing from 1 to 4 carbon atoms as methyl, ethyl, propyl or preferably *tert*-butyle, a nitro group, a $(C_1-C_4)$alkoxy group and an halogen atom, as chore, bromine or iodine,

- an « arylalkyl group » means preferably an aryl group appended to an alkyl group containing from 1 to 4 carbon atoms,

- an « alkoxycarbonyl group » means preferably an alkoxy group containing from 1 to 4 carbon atoms appended to a carbonyl group, as methoxycarbonyl,

- an « heteroaryl group » means preferably an aryl group containing from 1 to 3 heteroatoms, as nitrogen, sulphur or oxygen, including pyridyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, etc,

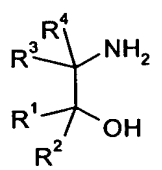
- an « heterocycle » or « heterocyclic group » means preferably a 5- or 6-membered ring containing from 1 to 3 heteroatoms as sulphur, nitrogen, or oxygen. This definition also contains bicyclic rings where a heterocyclic group as previously defined is fused with a phenyl group, a cyclohexan group or any other heterocycle. Among heterocyclic groups imidazolyl, indolyl, isoxazolyl, furyl, pyrazolyl, thienyl, etc, may be cited,

- an « heteroarylalkyl group » means preferably an heteroaryl group appended to an alkyl group containing from 1 to 4 carbon atoms, preferably methyl,

- an « heterocyclalkyl group » means preferably an heterocyclic group appended to an alkyl group containing from 1 to 4 carbon atoms, preferably methyl, as 4-imidazolylmethyl.

More particularly, the ligand of formula (II) may be derived from:

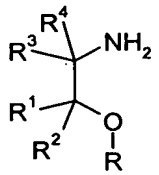
- an amino-alcohol of formula (III)



(III)

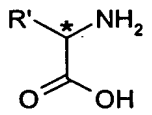
wherein $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$ and $\mathbf{R_4}$ are as previously defined. Among amino-alcools of formulae (III) L- (*S*-(+)-) or D-valinol (*R*-(-)-2-amino-3-methyl-1-butanol), *R*-*tert*-leucinol (*R*-(-)-2-amino-3,3-dimethyl-1-butanol), *S*-*tert*-leucinol (*S*-(+)-2-amino-3,3-dimethyl-1-butanol), and (1*S*,2*R*)-(-)- or (1*R*,2*S*)-(+)-1-amino-2-indanol, may be cited,

- an amino-ether of formula (IV)


(IV)

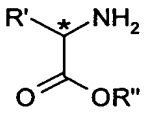
wherein $\mathbf{R}$, $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$ and $\mathbf{R_4}$ are as previously defined.

- an amino acid of formula (V)


(V)

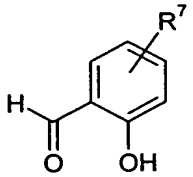
wherein $\mathbf{R'}$ takes the definition of $R_3$ or $R_4$ as previously given. Among the aminoacids of formulae (V) L-valin or D-valin, L-phenylalanin or D-phenylalanin, L-methionin or D-methionin, L-histidin or D-histidin and L-lysin or D-lysin may be cited.

- an amino-ester of formula (VI)


(VI)

wherein $\mathbf{R'}$ takes the definition of $R_3$ or $R_4$ as previously given and $\mathbf{R''}$ takes the definition of R.

Preferably, in order to obtain particularly advantageous ligands, i.e. Schiff bases, these amino-alcohol, amino-ether, amino acids and amino-esters respectively of formulae (III), (IV), (V) and (VI) are reacted with an aldehyde of salicylic acid of formula (VII)


(VII)

wherein $R_7$ represents from 1 to 2 substituents chosen independently ones of the others among an hydroxyl group, a linear or branched alkyl group containing from 1 to 4 carbon atoms such as methyl, ethyl, propyl or preferably *tert*-butyl, a nitro group, a $(C_1-C_4)$alkoxy group and an halogen atom, such as chlorine, bromine or iodine.

In the framework of the present invention, ligands of formula (II) are particularly preferred, said ligands are derived from an amino-alcool of formula (III), for which
$R_5$ and $R_6$ represents together with the nitrogen atom a double bond -N=CHAr, wherein **Ar** is an aryl group containing from 1 to 3 substituents and at least an hydroxyl group, **Ar** being preferably a phenyl group,
$R_1$ and $R_3$, or $R_2$ and $R_4$, represent a hydrogen atom, whereas $R_2$ and $R_4$, or $R_1$ and $R_3$, respectively, are, independently ones of the others, linear or branched alkyl groups containing from 1 to 6 carbon atoms, preferably a *tert*-butyl group or form together a carbon cycle of 5 or 6 carbon atomes or a bicyclic ring system of 9 or 10 carbon atoms, wherein one of the cycles may be aromatic, preferably indanyl.

According to the present invention, a ligand may be advantageously chosen according to the catalyst used, and for example in the case of tungsten, a ligand may be used according to the seeked enantiomer, said ligand:

- belonging to the family of quinquina alcaloids as quinine, quinidine, dihydroquinidine (DHQD) or dihydroquinine (DHQ),

- being derived from quinquina alcaloids as hydroquinine 2,5-diphenyl-4,6-pyridinediyl diether $(DHQ)_2$-PYR or hydroquinidine 2,5-diphenyl-4,6-pyridinediyl diether $(DHQD)_2$-PYR.

In the case of a vanadium-based catalyst, a ligand represented by formula (II) above is preferably used, containing a substituant on the nitrogen atom, and for example a Schiff base derived from a substituted aldehyde of salicylic acid and from a chiral amino-alcool.

Generally, one uses preferably, in the case of a vanadium-based catalyst taken as vanadium acetylacetonate, a ligand derived form an amino-alcool or an amino-ether respectively of formulae (III) or (IV) as defined above. To the contrary, in the case of a vanadium-based catalyst taken as vanadium sulphate, a ligand derived from an amino acid or an amino ester respectively of formulae (V) or (VI) as defined above is preferably used.

Thus in the case of a vanadium-based catalyst, preferably taken as vanadium acetylacetonate, ligands 2,4-di-*tert*-butyl-6-[1-*R*-hydroxymethyl-2-methyl-propylimino)-methyl]-phenol and its isomer 2,4-di-*tert*-butyl-6-[1-*S*-hydroxymethyl-2-methyl-propylimino)-methyl]-phenol which allow to selectively orientate the reaction to the seeked enantiomer, are particularly preferred. Thus the use of 2,4-di-*tert*-butyl-6-[1-*R*-hydroxymethyl-2-methyl-propylimino)-methyl]-phenol allows to selectively orientate the oxidation reaction of the 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine to obtain the *S*-tenatoprazole, as indicated below.

In the same way, always in the case of a vanadium-based catalyst, preferably taken as vanadium acetylacetonate, ligand (1*R*, 2*S*)-1-[2-hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol, derived from amino-indanol as amino-alcool, is particularly preferred.

Thus, the use of said ligand allows to selectively orientate the oxidation reaction of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine, to selectively obtain the *S*-tenatoprazole, as indicated below.

Under the operating conditions, the ligand is preferably tridentate and forms with the metal catalyst an asymmetric complex where the metal is oxidized by the oxidant.

According to a characteristic feature of the present invention, the reaction may be carried out in a solvent, preferably in a mixture of solvents, in a neutral or weakly basic medium, by selecting a sulphide specific solvent and a

ligand specific solvent, selected from the group consisting of methanol, tetrahydrofuran, methylene chloride, acetonitrile, toluene, acetone, chloroform, DMF (dimethylformamide) or NMP (N-methylpyrrolidinone), alone or in admixture. The base possibly used may be a tertiary amine such as pyridine, di-isopropylethylamine or triethylamine.

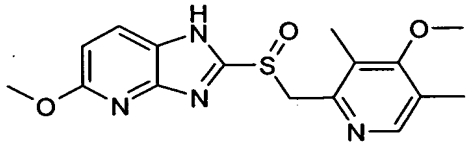
According to an alternative, the method may be implemented without the addition of a base, but it is preferable to avoid working in an acid medium as this could cause a degradation of the final product.

It is more particularly advantageous, according to the invention, to use the vanadium-based catalyst and the ligand in acetonitrile solution, whilst the sulphide is dissolved in a chlorinated solvent such as methylene chloride, and then the two solutions are mixed, and the oxidation is carried out.

The oxidation reaction is easily conducted at low temperatures or at room temperature. It might be advantageous to induce it at a temperature between 0 and 10°C and preferably of about 4 to 5°C in order to promote the enantioselectivity.

The method of the invention is particularly advantageous in as much as the oxidant and the catalyst are both widely commercially available, cheap and easy to process. Moreover, the catalyst can be used efficiently and in very small quantities. The yield of enantiomers obtained is excellent, and, moreover, the catalyst and the ligand can usually be recycled under good conditions without any loss of the enantiomeric excess.

The method of the present invention is particularly advantageous in the preparation of the enantiomers of tenatoprazole which can be represented by the following general formula:



Thus, according to the method of the invention, a very advantageous enantioselective oxidation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine by hydrogen peroxide in the presence of tungsten trioxide and of $(DHQD)_2$-PYR can be performed in order to obtain (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]imidazo[4,5-b]pyridine.

More particularly, it has been noted that the oxidation of the above sulphide allows for the (-) enantiomer, having the S-configuration, to be obtained with excellent conditions of purity and yield when a vanadium-based catalyst is used in association with a ligand consisting of 2,4-di-tert-butyl-6-[1-*R*-hydroxy-methyl-2-methyl-propylimino)-methyl]-phenol or (1*R*, 2*S*)-1-[2-hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol in acetonitrile solution, whilst the sulphide is in methylene chloride solution, or in acetone or in NMP respectively.

Conversely, the (+) isomer, having the R-configuration, can also be obtained with excellent conditions of selectivity and yield by using 2,4-di-tert-butyl-6-[1-*S*-hydroxy-methyl-2-methyl-propylimino)-methyl]-phenol or (1*S*,2*R*)-1-[2-hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol as a ligand.

The (-) and (+) enantiomers of tenatoprazole may be used under the form of salts, and particularly of alkaline metal salt or earth-alkaline metal salt, and for example under the form of a sodium, potassium, lithium, magnesium or calcium salts. These salts can be obtained from the (-) or (+) enantiomer of tenatoprazole which has previously been isolated by salification according to the standard method of the technique, for example by the action of basic mineral reagents comprising alkaline or earth-alkaline counter-ions.

Of course, the (-) and (+) enantiomers can be obtained in a pure optical form simply from the racemic mixture, using any appropriate method of separation, by preparative column chromatography, for example chiral or HPLC chromatography. The enantiomers thus obtained can be used for controls. "Pure

optical form" means that the (-) enantiomer is substantially free from the (+) enantiomer, or only contains traces of it and vice versa. If necessary, a salification by a base is then performed in an appropriate solvent, in order to form a salt, and particularly an alkaline or earth-alkaline metal salt.

The principle of the chiral chromatography method is well known and is based on the difference in affinity existing between the (+) and (-) enantiomers and the chiral selector of the stationary phase. This method enables the separation of the enantiomers with a satisfactory yield.

The (-) enantiomer of tenatoprazole corresponds to (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]imidazo[4,5-b]pyridine, or (-)-tenatoprazole. This form can be determined by optical rotation measurements using standard techniques. Thus, the optical rotation angle of the (-)-tenatoprazole is levo-rotatory in dimethylformamide an in acetonitrile, and its melting point is 130° (decomposition).

In the case of chiral separation of tenatoprazole, the racemic mixture used as the starting material can be obtained using known methods, for example according to the method described in Patent No. EP 254.588. Thus it can be prepared using an oxidizing agent, such as perbenzoic acid, to treat the corresponding sulphide arising from the condensation of a thiol and a pyridine, preferably in the presence of a base such as potassium hydroxide in an appropriate solvent, for example, ethanol, under heating.

In the treatment of the disorders mentioned below, the (-) and (+) enantiomers of tenatoprazole can be administered in standard forms adapted to the chosen administration route, for example per oral or parenteral route, preferably per oral or intravenous route.

For example, tablet or capsule formulations containing either one of the (-) and (+) enantiomers of tenatoprazole as an active substance, or else oral solutions or emulsions or solutions for parenteral administration containing a tenatoprazole salt with a pharmaceutically acceptable standard

substrate, can be used. The enantiomer salt of tenatoprazole can be chosen among the sodium, potassium, lithium, magnesium or calcium salts for example.

The (-) and (+) enantiomers of tenatoprazole obtained using the method of the present invention can be used in the manufacturing of drugs for the treatment of digestive disorders, and in particular of those where the gastric acid inhibition must be strong and prolonged, in the treatment of the symptoms and lesions of gastro-oesophageal reflux, digestive bleeding resistant to the other proton pump inhibitors.

The dosage regimen is determined by the physician according to the patient's state and the severity of the condition. It is generally between 10 and 120 mg, preferably between 20 and 80 mg, of (-) or (+) enantiomer of tenatoprazole per day.

Examples of the preparation of enantiomers are described below in order to illustrate the present invention without limiting its applications.

**Example 1**

Preparation of (*S*)-(-)-tenatoprazole

10 g of $WO_3$, 73 g of $(DHQD)_2$-PYR, 3.5 L of THF and 330 g of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio] imidazo[4,5-b]pyridine maintained under agitation at a temperature comprised between 4 and 5°C, are placed in a 5 L flask, and 120 mL of hydrogen peroxide at 30% are added thereto. The reaction medium is maintained under agitation for 48 hours. The catalyst is then filtered and the filtrate is diluted into 10 L of methylene chloride at room temperature.

The organic phase is washed with water, then dried and concentrated under reduced pressure. 242 g of the desired enantiomer are obtained, with an enantiomeric excess above 90% (70% yield).

A recrystallization is performed in the methanol/water or DMF/ethyl acetate mixture and the enantiomer is obtained with an enantiomeric excess superior to 99%. The enantiomeric

excess is determined by high pressure liquid chromatography with a CHIRALPAK AS-H 20 µm (250 x 4,6 mm) column at 25°C, the eluent is acetonitrile (1 mL/min) and the detection is performed by U.V. spectroscopy at 305 nm. The retention time of the (*S*)-(-) isomer equals 7.7 min, and that of the (*R*)-(+) isomer equals 5.2 min.

$T_F$ : 129-130°C

$[\alpha]^{20}_D$ : -186.6 (c 0,1, DMF)

Elementary analysis :

| Elements | C | H | N | S |
|---|---|---|---|---|
| theory | 55.48 | 5.24 | 16.17 | 9.26 |
| observation | 55.66 | 5.22 | 16.16 | 9.37 |

UV Spectrum (methanol-water): $\lambda_{max}$: 272 nm ($\varepsilon$ = 6180), 315 nm ($\varepsilon$ = 24877).

Infra-red (KBr) : 3006, 1581, 1436, 1364, 1262, 1026, 1040 and 823 $cm^{-1}$.

RMN $^1H$ (DMSO $d_6$, reference : TMS) $\delta$ (ppm) : 2.20 (s, 6H), 3.70 (s, 3H), 3.91 (s, 3H), 4.69-4.85 (m, 2H), 6.80 (d, *J* 8.5 Hz, 1H), 7.99 (d, *J* 8.5 Hz, 1 H), 8.16 (s, H), 13.92 (s, 1H).

RMN $^{13}C$ (DMSO $d_6$, reference : TMS) $\delta$ (ppm) : 13.2 ; 15.0 ; 56.6 ; 60.8 ; 62.6 ; 107.2 ; 129.5 ; 130.4 ; 131.9 ; 135.1 ; 150.5 ; 151.4 ; 156.9 ; 160.7 ; 163.0 ; 166.6.

**Example 2**

Preparation of (*R*)-(+)-tenatoprazole

Using the same conditions as set out in Example 1, but replacing $(DHQD)_2$-PYR by $(DHQ)_2$-PYR, 120 mL of hydrogen peroxide are caused to react with the same quantity of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-imidazo[4,5-b]pyridine as set out in Example 1 and using the same catalyst.

The desired (+) enantiomer is thus obtained with an enantiomeric excess above 99%, after recrystallisation in a DMF / ethyl acetate mixture.

The rotatory power measured with a polarimeter in dimethyl formamide is $[D]^{20}_D = +186°$.

The physical and spectroscopic constants of (R)-(+)-tenatoprazole are identical to those of (S)-(-)-tenatoprazole, except for the specific rotatory power : $[\alpha]^{20}_D$ : +185.9 (c 0.1, DMF).

**Example 3**

Preparation of (*S*)-(-)-omeprazole (esomeprazole)

Using the operating conditions of Example 1, and using 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-1H-benzimidazole instead of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine, the desired product (esomeprazole) is obtained with an enantiomeric excess near 90% (72% yield).

The product obtained complies with the analytical data available in the literature.

**Example 4**

Preparation of (*S*)-(-)-tenatoprazole

3 L of methylene chloride, and then 360 g of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine are introduced in a 5 L flask. The mixture is left under stirring at room temperature for 30 minutes.

700 ml of acetonitrile, 5.22 g of 2,4-di-tert-butyl-6-[1-*S*-hydroxymethyl-2-methyl-propylimino)-methyl]-phenol, and then 2.90 g of vanadyl acetylacetonate are dropped one after the other in a 2 L flask. The mixture is kept under stirring at room temperature. After 30 minutes under stirring, this mixture is added to the preceding one.

135 ml of hydrogen peroxide at 30% are added to this mixture under stirring for 20 h at room temperature. After separation of the aqueous phase, the organic phase is washed twice with water, then dried and concentrated under reduced pressure. 283 g of the desired enantiomer are obtained, with an enantiomeric excess superior to 80% (75% yield). Two

successive recrystallizations are performed in a methanol-/water or DMF/ethyl acetate mixture and the enantiomer is obtained with an enantiomeric excess higher than 99%.

$T_F$ : 127.5°C

$[\alpha]^{20}_D$ : -182 (c 0.1, DMF)

**Example 5**

Preparation of (*R*)-(+)-tenatoprazole

The instructions from Example 4 are followed but 2,4-di-tert-butyl-6-[1-*R*-hydroxymethyl-2-methyl-propylimino)-methyl]-phenol is replaced by 2,4-di-tert-butyl-6-[1-*S*-hydroxymethyl-2-methyl-propylimino)-methyl]-phenol.

The desired enantiomer is thus obtained.

$[\alpha]^{20}_D$: +185,9 (c 0,1, DMF).

**Example 6**

Preparation of (*S*)-(-)-tenatoprazole

1,2 L of NMP, and then 240 g of 5-methoxy-2-[[4-methoxy-3,5-dimethyl]-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine are introduced in a 5 L flask. The mixture is left under stirring at room temperature for 1h30.

18 mL de NMP, 2,9 g of (1*R*, 2*S*)-1-[2-hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol, and then 1,9 g of vanadium acetylacetonate are introduced in this order in a 50 mL round bottom flask. The mixture is stirred at room temperature. After 1h30 of stirring, the solution is added into the reaction mixture.

Under stirring, 95 mL of hydrogen peroxide at 30% are added to this mixture for 20 hours at room temperature. The reaction mixture is precipitated by adding 500 mL of water.

The precipitate is recovered by filtration, then it is taken in 5 L of chloroform. The organic phase is washed twice qith water, then dried and concentrated under reduced pressure. 126 g of the desired enantiomer are obtained with an enantiomeric excess superior to 30% (yield 50%). Several crystallizations in a DMF / ethyl acetate mixture are carried

out and the enantiomer is obtained with an enantiomeric excess superior to 99%.

**Example 7**

Preparation of (*S*)-(-)-tenatoprazole

3.7 L of acetone and then 30 g of 5-methoxy-2-[[4-methoxy-3,5-dimethyl]-2-pyridyl)methyl]thio]imidazo[4,5-b]-pyridine are introduced into a 10 L flask. The mixture is left undder stirring for 30 minutes at room temperature.

30 mL of acetonitrile, 1,66 g of (1*R*, 2*S*)-1-[2-hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol, and then 1,19 g of vanadium acetylacetonate are introduced in a 100 mL round bottom flask. The mixture is stirred at room temperature. After stirring for 1h30, this suspension is added into the reaction mixture.

Under stirring, 10 g of urea-$H_2O_2$ dissolved in 7 mL of water and 50 mL of acetone are added for 6 hours to this mixture. Then, the mixture is left at room temperature for 12 hours. A sodium metabisulfite solution is added, then a 20% ammonia solution and acetone is concentrated. After washing with 100 mL of chloroform, the aqueous phase is collected and then neutralized with acetic acid. An extraction with 200 mL of chloroform is carried out twice. After separation of the aqueous phase, the organic phase is dried and concentrated under reduced pressure. 19 g of the desired enantiomer are obtained with an enantiomeric excess superior to 50% (yield 60%). Several crystallizations are carried out in a DMF / ethyl acetate mixture, and the enantiomer is obtained with an enantiomeric excess superior to 99%.

**Example 8**

Preparation of (*S*)-(-)-tenatoprazole

4 L of acetone and then 30 g of 5-methoxy-2-[[4-methoxy-3,5-dimethyl]-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine are introduced into a 10 L flask. The mixture is left undder stirring for 30 minutes at room temperature.

25 mL of acetonitrile, 1,66 g of (1*R*, 2*S*)-1-[2-hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol, and then 1,19 g of vanadium acetylacetonate are introduced in this order in a 100 mL round bottom flask. The mixture is stirred at room temperature. After stirring for 1h30, this suspension is added into the reaction mixture.

Under stirring, 30 g of sodium sulfate, 10 g of urea-$H_2O_2$ dissolved in 7 mL of water and 50 mL of acetone are added for 6 hours to this mixture. Then, the mixture is left under stirring at room temperature for 12 hours. A sodium metabisulfite solution is added, then a 20% ammonia solution and acetone is concentrated. After washing with 100 mL of chloroform, the aqueous phase is collected and then neutralized with acetic acid. An extraction with 200 mL of chloroform is carried out twice. After separation of the aqueous phase, the organic phase is dried and concentrated under reduced pressure. 20.1 g of the desired enantiomer are obtained with an enantiomeric excess superior to 65% (yield 64%). Several crystallizations are carried out in a DMF / ethyl acetate mixture, and the enantiomer is obtained with an enantiomeric excess superior to 99%.